Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Protocol development for neonatal trials: Points to consider for pharmacovigilance

V 1.0, 22 March 2021

Description	This tool gives points to consider concerning pharmacovigilance and risk managment at the time neonatal protocol development
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Drug safety, Pharmacovigilance, Risk management

Authors: Beate Aurich, Valéry Elie, Naura Mahmoudi, Evelyne Jacqz-Aigrain

Disclaimer: **Sponsors and researchers unfamiliar with clinical trials in neonates and/or neonatology are advised to seek expert advice due the complexity of neonatology.**

Correspondence email: pedcrin@ecrin.org

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

Introduction

During protocol development drug safety is considered in multiple sections such as the objectives, exclusion criteria as well as safety data collection, reporting and analysis and follow-up.[1] Standard regulatory obligations for safety data collection and analysis, reporting of adverse drug reactions and pharmacovigilance apply regardless of the age of the study population of a clinical trial.[1-4]

Drug safety and neonatal protocol development: Points to consider

All available safety data of the study drug is combined with the specificities of the neonatal study population at the time of the development of the protocol.[5,6] To facilitate this process it can be helpful to list the identified and potential risks of the study drug and how these can be analysed and managed.[4] This data review informs protocol sections related to safety and risk management such as exclusion criteria, study procedures for patient monitoring, dose reduction, dose holding and stopping criteria, data collection, follow up and data analysis.[4] An understanding of pharmacokinetics and pharmacodynamics is important in order to anticipate and detect dose related toxicity, interactions and off-target adverse drug reactions.[7,8]
Figure 1 illustrates how the population specific drug safety profile informs risk management and pharmacovigilance in neonatal clinical trial protocols.[9]

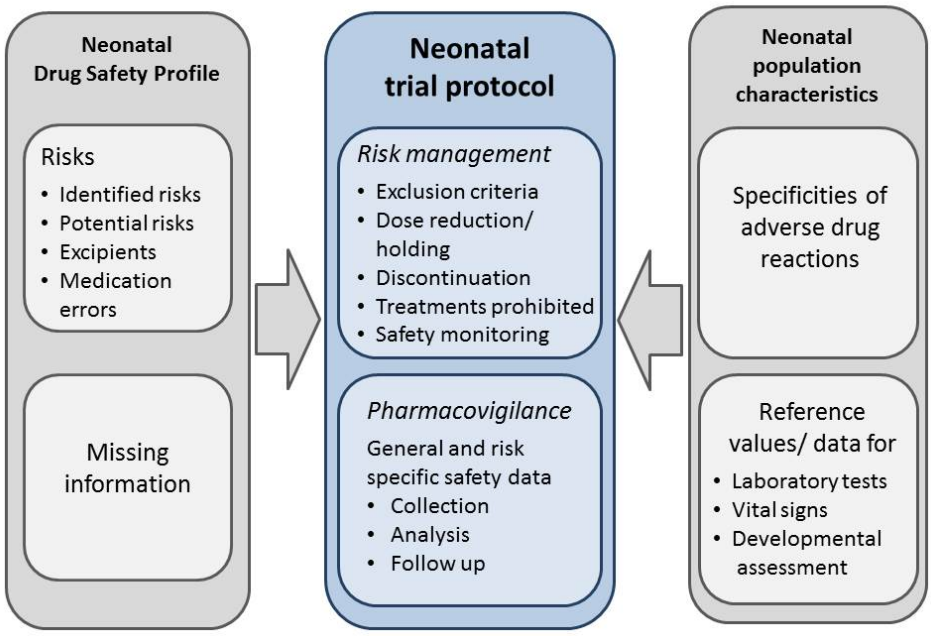

Figure 1. Link between neonatal safety profile, population characteristics of neonatal population and drug safety related protocol sections (adapted from Aurich et al. 2019)

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

For example, patients with pre-existing severe renal impairment may be excluded from a trial for a drug known to cause renal impairment. Data collection for such a drug may include regular monitoring of the renal function and stopping rules may specify that patients with new onset or worsening renal impairment need to discontinue the study drug. Follow up after discontinuation may specify that the renal function should be monitored until full recovery. Data analysis may, for example, describe the time to onset for renal impairment, the severity, seriousness and outcome of renal impairment and any risk factors such as cumulative dose and comedications. Table 1 lists protocol sections where drug safety information may need to be considered.

Conclusions

A comprehensive, up-to-date safety data review of the study drug combined with an understanding of the specificities of the neonatal population is required in order to optimise the development of safety relevant protocol sections. This tailored approach helps to proactively manage risks associated with study drug treatment, contributes to good quality safety data collection supporting a data driven assessment of benefit-risk. Due to the complexities of drug safety it is recommended to include an experienced pharmacovigilance physician, ideally with neonatal experience, in the protocol development process.

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

Competing interests

All authors consider not having any competing interests for this tool. BA has worked for GlaxoSmithKline between October 2006 and September 2009 and holds company shares. Between October 2009 and May 2015 she has worked for Novartis.

References

1. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). ICH Harmonised Tripartite Guideline – Guideline for Good Clinical Practice E6(R1). Current Step 4 version10 June 1996, Geneva. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline .pdf
2. European Council (EC). Amendment to Regulation (EC) No 726/2004 as regards pharmacovigilance. Official Journal of the European Union, Strasbourg 25 October 2012, L 316/38; 14.11.2012. Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:316:0038: 0040:EN:PDF
3. European Council (EC). Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmaco-vigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. Official journal of the European Union, Strasbourg 15 December 2010, L 348/1; 31.12.2010. Available at: https://eur-lex. europa.eu/LexUriServ/LexUriServ. do?uri=OJ:L:2010:348:0001:0016:EN:PDF
4. European Medicines Agency (EMA). Good pharmacovigilance practices. London 2018. Accessed 11/12/2018. Available at: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/ pharmacovigilance/good-pharmacovigilance-practices
5. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). ICH Tripartite Guidelines - Clinical investigation of medicinal products in the pediatric population E11, Current Step 4version, 20 July 2000, Geneva. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guidelines.pdf
6. Manuck TA, Rice MM, Bailit JL, Grobman WA, Reddy UM, Wapner RJ, et al. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol. 2016 Jul;215(1):103.e1-103.e14. doi:10.1016/j.ajog.2016.01. 004.
7. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med. 2003 Sep 18;349(12):1157-67. doi: 10.1056/NEJMra035092.
8. World Health Organization (WHO). Promoting safety of medicines for children. WHO library, ISBN 978-92-4-156343-7, Geneva 2007. Available at: https://www.who.int/medicines/publications/ essentialmedicines/Promotion_safe_med_ childrens.pdf
9. Aurich B, Elie V, Jacqz-Aigrain E. P11 Neonatal and paediatric protocol development and drug safety: points to consider for risk management and safety data collection. Archives of Disease in Childhood 2019;104:e21-e22. doi: 10.1136/archdischild-2019-esdppp.50.

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

Table 1. Neonatal protocol development and phamracovigilance: Points to consider (not exhaustive)

Protocol section	Examples of information related to neonatal drug safety profile
Introduction	Neonatal safety profile (identified and potential risks in neonates)[1-4] Benefit-risk balance in neonates[5]
Objectives	Safety is often a secondary objective[3,4]
Exclusion criteria	Based on neonatal safety profile (identified and potential risks in neonates) and potential confounding factors for drug response (e.g. live-threatening major congenital malformations)[1-5]
Discontinuation, dose holding, dose reduction criteria	Based on neonatal pharmacokinetics, pharmacodynamics and safety profile (identified and potential risks in neonates)[1-6]
Study procedures	Data collection on risk factors and confounding factors for adverse drug reactions based on neonatal safety profile (identified and potential risks in neonates)[1,5] Needs to take ethical limitations of data collection into account[5,7-9]
Case report form (CRF)	Design based on data collection as per study procedures and regulatory obligations for adverse event reporting[1,2]
Adverse event reporting	As per standard regulations[1,2,5,8]
Follow up	Based on neonatal safety profile (identified and potential risks in neonates)[1,2,5,9]
Safety data analysis plan	Based on neonatal safety profile (identified and potential risks in neonates)[1,2,5]
DSMB review	As requested by DSMB +/- based on safety data analysis plan[1,2,5,10]

References:

1. **International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH).** ICH harmonised tripartite guideline – Pharmacovigilance planning E2E, Current Step 4, version 18 November 2004. Available at: https://database.ich.org/ sites/default/files/E2E_Guideline.pdf
2. **European Medicines Agency (EMA)**. Guideline on good pharmacovigilance practices (GVP)Product

   - or Population-Specific Considerations IV: Paediatric population. EMA/572054/2016, 25 October 2018. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-iv_en-0.pdf
3. **European Medicines Agency (EMA)**. Guideline for good clinical practice E6 (R2), Step 5, EMA/ CHMP/ICH/135/1995 Committee for Human Medicinal Products. London, 1 December 2016. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
4. **Begg** C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA1996;276:637-9.
5. **European Medicines Agency (EMEA)**, Committee for Medicinal Products for human use (CHMP), Paediatric Committee (PDCO). Guidelines on the investigation of medicinal products in the term and preterm neonate. Doc. Ref. EMEA/536810/2008, London, 25 June 2009. Available at: https://www. ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-medicinal-products-term-preterm-neonate-first-version_en.pdf
6. **Kearns** GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med. 2003 Sep 18;349(12):1157-67. doi: 10.1056/NEJMra035092.
7. **Howie** SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011 Jan 1;89(1):46-53. doi: 10.2471/BLT.10.080010.
8. **European Medicines Agency (EMA)**. Guideline on good pharmacovigilance practices (GVP)

   Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). EMA/873138/2011Rev 2*, 28 July 2017. Available at: https://www.ema. europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf
9. **European Medicines Agency (EMA),** Committee for Human Medicinal Products (CHMP). ICH E11 (R1) guideline on clinical investigation of medicinal products in the pediatric population, Step 5. EMA/CPMP/ICH/2711/1999 Committee for Human Medicinal Products, 1 September 2017. Available at: https://www.ema.europa.eu/en/documents/ scientific-guideline/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1_en.pdf
10. **European Medicines Agency (EMEA),** Committee for Medicinal Products for human use (CHMP). GUIDELINE ON DATA MONITORING COMMITTEES. Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr, London, 27 July 2005. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046